*Original Articles*

# Pregnancy and H1N1 infection in Southeast Turkey

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## Abstract

Introduction: H1N1 Influenza made a great impact a worldwide, as well as in Turkey, in 2009. Clinical experiences have shown that it had a more serious prognosis in pregnant women. In this report, we summarize the cases of 16 pregnant women with H1N1 Influenza.

Methodology: The study included 16 pregnant women hospitalized in Dicle University Hospital with complaints of fever, sore throat, cough and myalgia between October and December 2009. The diagnosis of pandemic H1N1 Influenza was confirmed on nasopharyngeal specimens using real-time reverse-transcriptase polymerase chain reaction (RT-PCR) in all patients. Patients who had the same complaints but were not diagnosed as H1N1 Influenza were excluded. The epidemiological, clinical, diagnostic, and outcome features of the patients were recorded.

Results: The median age of the patients was 27 years (range 18-41 years). The mean gestational age was 25.4 weeks (range 5-38 weeks). Two cases were twin pregnancy. Two cases had co-morbid diseases including asthma and anemia. The most frequent admission symptoms were fever in 13 cases (81%), cough in 12 cases (75%) and dyspnea in 6 cases (37,5%). Antiviral treatment (oseltamivir 75 mg p.o. bid) was applied in 15 cases. Four cases needed intensive care monitoring and two of them died (12.5%) because of severe respiratory insufficiency.

Conclusion: Patients with late gestational age, the presence of co-morbid disease, and multiple pregnancy have poor prognosis. Immediate intervention with antiviral treatment is associated with reduced severity of the disease and duration of hospital stay.

**Key words:** Influenza A virus; H1N1 subtype; pregnancy

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## Introduction

The H1N1 Influenza A pandemic started in Mexico in 2009 and then spread to the United States and other countries. On 11June 2009, phase 6 H1N1 Influenza A pandemic was declared by the World Health Organization (WHO) [1]. In Turkey, the first case was diagnosed on 15 May 2009, and the first related death was on 13 October 2009 [2]. By February 2010, the total number of deaths resulting from H1N1 Influenza A, for all of Turkey, was 627 [3]. According to data obtained from the Provincial Health Directorate of Diyarbakir, 20 pregnant women had H1N1 Influenza A, including 3 cases of death due to respiratory failure.

The novel H1N1 infection is usually associated with seasonal influenza-like symptoms such as fever, coughing, and sore throat. In some cases, gastrointestinal symptoms may occur such as nausea and diarrhoea. The infection may be a more severe prognosis for those in the following risk groups: those who are over 65 years of age; children under 5 years of age; pregnant women; health workers; patients with chronic diseases including lung disease, neurological disorders, and diabetes; and those receiving immunosuppressive therapy [6]. Experiences related to this infection showed that the 2009 H1N1 Influenza A caused a notable increase in the number of hospitalizations and had the potential to be a more severe disease for pregnant women than for non-pregnant women [7]. In this study, we examined the demographic features, clinical course, treatment modalities, and maternal and fetal outcomes of 16 pregnant women with the H1N1 Influenza A.

## Methodology

Dicle University Hospital is a 1,050-bed facility in Diyarbakir, Turkey. The hospital is the largest health centre in the southeastern region of Turkey, has a catchment area of approximately three million people, and provides primary, secondary, and tertiary care. Every year, 26,000 patients are seen in the emergency department. The Flu Clinic was created during the H1N1 Influenza A pandemic to deal with the heightened risk of infection spreading within the hospital. The hospital was also the reference centre for other nearby hospitals during the pandemic.

A retrospective chart review was performed to collect the epidemiological data related to the H1N1 Influenza A cases. This study included all hospitalized pregnant women who had H1N1 Influenza A. This was confirmed by their nasopharyngeal specimens by real-time reverse-transcriptase polymerase chain reaction (rRT-PCR). All the cases were admitted to the Flu Clinic at Dicle University Hospital between October 1st and December 31st, 2009. This excludes some cases where the H1N1 Influenza A was suspected but not detected by the rRT-PCR. In this study, demographic features, clinical courses, treatment modalities, and the maternal and fetal outcomes of the patients were evaluated. The cases were classified as influenza or pneumonia according to the severity of the disease. Influenza was identified as influenza-like symptoms without signs of respiratory distress, pathological lung sounds, and infiltrates on a chest radiograph. Pneumonia was identified as fever, a non-productive or dry cough, tachypnea, dyspnea, wheezing, rhonchus, intercostals retractions, decreased respiratory sounds, hypoxia, acute respiratory distress, and alveolar opacities on a chest radiograph. Fever was considered to be a body temperature measurement over 37.5°C, measured from the axillaries fosse.

Patients were divided into three groups according to their initial treatment time. Patients in the early treatment group were treated with antiviral therapy within three days of the onset of symptoms. The late treatment group was treated five days after the onset of symptoms.

In addition, patients' socioeconomic statuses were classified according to their monthly income. Patients in a low socioeconomic group received less than 491 USD, which was the monthly minimum wage limit in Turkey.

This study was approved by the ethical committee at Dicle University and written consents were taken from each patient.

All statistical analyses were performed using SPSS for Windows 18.0 (IBM, Chicago, IL, USA). P values of $\leq 0.05$ were considered to be statistically significant. For characteristic features of cases, the numbers of the patients in each category were calculated. The nonparametric Mann-Whitney U and Kruskal Wallis tests were performed for characteristic and clinic factors affecting length of hospital stay. Factors associated with poorest clinical course were assessed by logistic regression analysis. Univariate analysis was performed and p values and odds ratio values were determined.

## Results

The median age of the patients was 27 years (range: 18-41 years). The median gestational age at hospital admission was 25.4 weeks (range: 5 to 38 weeks). Two cases had twin pregnancies (26th and 32nd weeks). The frequency of symptoms at the time of admission were as follows: fever in 13 cases (81%), coughing in 12 cases (75%), dyspnea in 6 cases (37.5%), myalgia in 3 cases (18%), rhinorrhea in 3 cases (18%), sore throat in 3 cases (18%), and palpitations in 1 case (6%). The body temperature for 10 patients was $\geq 38$°C.

Two cases were diagnosed as influenza caused by the H1N1 Influenza A virus, and 14 cases were diagnosed as pneumonia. In addition, the diagnosis of secondary bacterial pneumonia was made for cases with viral pneumonia, after evaluation of the physical examinations and laboratory findings. Oseltamivir was used for the patients' antiviral treatment. While 15 cases (93.8%) were treated with oseltamivir (75 mg p.o. 2x1), additional antibiotic therapy was initiated in 5 cases who were thought to have secondary bacterial pneumonia. Antibiotic therapy included ceftriaxone, cephoperazone-sulbactam, clarithromycin, and trimethoprim-sulfamethoxazole. The median period before initiating antiviral treatment was 4.3 days. Based on the initiation time of antiviral treatment, the patients were divided into three groups: those who received treatment within the first three days after the onset of symptoms, those who received treatment between four and five days after the onset of symptoms, and those patients who started treatment more than five days after the onset of symptoms. Patients receiving treatment within the first three days after the onset of symptoms were associated with a shorter hospital stay (a mean of 5.6 days), a better clinical course, and no secondary pneumonia as compared with the patients in the two other groups. The mean hospitalization period was 15.6 days for the cases who received antiviral drugs more than five days after the onset of symptoms. One case with pandemic H1N1 Influenza A was not treated by oseltamivir.

The median hospital stay was 8.4 days (range: 3 to 25 days). Factors prolonging patients' hospital stays were found to be young age of the mother, third trimester pregnancy, additional antibiotic therapy because of secondary pneumonia, initiation of treatment five days after the onset of symptoms, the presence of co-morbidities, and a lower socioeconomic status. The additional antibiotic therapy, initiation of treatment five days after the onset of symptoms, and a lower socioeconomic status were detected as statistically significant (Table 1). The strength of association between

**Table 1.** Characteristic features of 16 pregnant women with pandemic influenza A (H1N1) infection

| Features | Hospitalized Patients (Total 16) | Maternal Mortality (2 cases) | Hospital Stay (mean day) | *p* |
|---|---|---|---|---|
| **Maternal age (years)** | | | | |
| < 20 | 2 | | 10 | |
| 20-34 | 11 | 2 | 7.6 | 0.490 |
| ≥ 35 | 3 | | 7.7 | |
| **Gestational age (weeks)** | | | | |
| 0-13 | 2 | | 6.0 | |
| 14-28 | 7 | | 7.7 | 0.847 |
| > 28 | 7 | 2 | 9.0 | |
| **Gravidity** | | | | |
| One | 8 | 2 | 9.3 | 0.759 |
| 2-3 | 5 | | 6.0 | |
| > 3 | 3 | | 7.7 | |
| **Parity** | | | | |
| No | 8 | 2 | 9.3 | 0.539 |
| One | 4 | | 6.0 | |
| ≥ Two | 4 | | 7.7 | |
| **Number of fetuses** | | | | |
| Singleton | 14 | 1 | 8.2 | 0.522 |
| Twin | 2 | 1 | 6.0 | |
| **Antiviral medication** | | | | |
| No | 1 | 1 | 7 | |
| Oseltamivir only | 9 | | 8.5 | 0.05 |
| Additional antibiotherapy | 5 | 1 | 13.8 | |
| **Time¶ (day)** | | | | |
| ≤ 3 | 8 | | 5.6 | |
| 4-5 | 4 | 1 | 8.6 | 0.018 |
| >5 | 3 | | 15.6 | |
| **Co-morbid disease** | | | | |
| Asthma / Anemia (Hct < 30%) | 2 | | 17.5 | 0.078 |
| No | 14 | 2 | 6,6 | |
| **Socioeconomic status** | | | | |
| Normal | 9 | | 6 | 0.001 |
| Low | 7 | 2 | 11.5 | |

¶ **Time:** Initiation time of antiviral therapy after symptom onset

**Table 2.** Univariate analysis of factors associated with pandemic influenza A (H1N1) infection with poor clinical course

| Variables | P value | Odds Ratio |
|---|---|---|
| Age | 0.278 | 0.922 |
| Gravidity | 0.554 | 0.852 |
| Parity | 0.740 | 0.915 |
| Gestational age | 0.892 | 1.01 |
| Time¶ | 0.027 | 0.050 |
| Twin pregnancy | 0.882 | 1.12 |
| Co-morbid disease | 0.720 | 0.911 |
| Socioeconomic status | 0.009 | 4.8 |
| Dyspnea | 0.027 | 0.050 |
| Additional antibiotherapy | 0.008 | 4.03 |

¶ **Time:** Initiation time of antiviral therapy after symptom onset

**Table 3.** Demographics of cases requiring intensive care unit (ICU)

| | Maternal Age (years) | Gestational Age (weeks) | Risk Factor | Time¶ (days) | Hospital Stay (days) | Maternal Outcome |
|---|---|---|---|---|---|---|
| **Case 1** | 34 | 32 wk | Twin pregnancy | no | **7** | died |
| **Case 2** | 41 | 27 wk | - | 10 | 10 | recovery |
| **Case 3** | 27 | 33 wk | Asthma | 10 | 25 | recovery |
| **Case 4** | 21 | 32 wk | - | 5 | 12 | died |

¶ **Time:** Initiation time of antiviral therapy after symptom onset

patients with poorest clinical course and various features was not equally distributed (see odds ratios described in Table 2).

Four of the cases were admitted to the intensive care unit (ICU) because of acute respiratory distress syndrome (ARDS). Two cases in the ICU died. When compared with other patients, those in the ICU had additional co-morbidities such as asthma, twin pregnancy, advanced age for pregnancy, and late access or inability to access treatment. Characteristic features of cases monitored in the ICU are shown in Table 3.

With regard to obstetric complications, two cases developed fetal distress and two women had to terminate their pregnancies prematurely. Four women out of 16 delivered during their in-patient monitoring period because of the H1N1 infection. The influenza infection was not detected in any of the babies. We managed to contact nine of the patients discharged from the hospital after recovery; two cases delivered prematurely and one delivered a low birth-weight infant (2500 g) to term. As far as we know, the H1N1 Influenza infection was not detected in any of the babies born in an external medical centre.

## Discussion

Although the H1N1 Influenza infection causes symptoms in pregnant women similar to those observed in seasonal influenza (fever, coughing, sore throat, nasal discharge), when compared with the normal population, more severe symptoms and a greater number of complications have been observed in pregnancy [4]. In our study, symptomsmost frequently encountered were fever (81%), coughing (75%), and dyspnea (37.5%). Dyspnea attracted our attention as the most significant symptom. Six cases with dyspnea were in their late gestational ages, and all of them had pneumonia. Four of them received follow-up treatment in the ICU because of ARDS, and two of the women died. Due to a lack of a control group in our study, we could not determine if any difference existed between the complaints reported by pregnant and non-pregnant patients with H1N1.

However, Jamieson *et al*. reported that fever, sore throat, headache, and dyspnea are the most frequently seen symptoms of pregnant women with H1N1. The same complaints were also observed in non-pregnant women, excluding dyspnea, which was more common in pregnant women [5].

Various studies have revealed that an influenza infection leads to more serious complications in pregnant women, and significantly higher rates of respiratory tract infection occur in young pregnant women who have not previously encountered a new H1N1 Influenza strain [6,7]. In our study, complications seen in pregnant women with H1N1 Influenza were secondary bacterial pneumonia and ARDS. Cases who developed ARDS were followed up in the ICU, but two patients died. Complications were especially common when associated with an advanced gestational age, twin pregnancies, co-morbidities, and a lower socioeconomic status. Also, certain conditions associated with increased risk of complications for seasonal influenza (pulmonary, cardiovascular, hepatic, hematologic, neurologic and neuromuscular co-morbidities; metabolic disorders or immunosuppression; long-term aspirin therapy in persons aged ≤ 18 years; and/or being a resident of a nursing home or other chronic-care facility) might have similar effects in pregnant women with Influenza H1N1 [5,8,9]. We believe that increased rates of complications relatedto H1N1 Influenza can be attributed to alterations to the immune, cardiovascular, and respiratory systems [10]. In pregnancy, the humoral response, the antibody-mediated immune response provided by means of T helper type 2 lymphocytes, is prominent and useful for the suppression of rejection developed against fetal antigens. However, as a counteraction, cell-mediated immunity regulated by T helper type 1 lymphocytes, which form the basis of the defense mechanism that fights specifically against intracellular pathogens such as viruses, are suppressed [11]. In addition to alterations in the immune system, pulmonary changes such as an increased heart rate and oxygen consumption, and a decrease in tidal volume, might adversely

contribute to the severity of influenza infections in pregnant women [12].

The neuraminidase inhibitors oseltamivir and zanamivir have been used in the treatment of H1N1 Influenza A as an antiviral agent. Both oseltamivir and zanamivir are pregnancy category C group drugs, and any adverse effects related to their usage in pregnancy have not yet been reported [13]. In all of our cases but one oseltamivir was used as an antiviral agent. For the first case of antiviral therapy, because of our lack of experience managing the H1N1 infection, we waited for RT-PCR test results and the patient was lost because of ARDS before the test results came back. Faster clinic recovery was observed in cases that started to receive treatment at an earlier phase. This was especially noticeable for cases that began to receive treatment within 72 hours of the onset of symptoms; shorter hospitalization periods were detected, and also secondary bacterial pneumonia did not develop in these patients. The US Centers for Disease Control and Prevention (CDC) indicated the usefulness of antiviral treatment initiated within the first 48 hours after the onset of symptoms [14]. Therefore, treatment should not be delayed because of safety concerns related to antiviral drug usage in pregnancy. Moreover, an increase in obstetric and fetal complications related to H1N1 Influenza can be seen. In our study, two cases of premature delivery and two cases of fetal distress developed, which were thought to be related to the H1N1 infection. With regard to obstetric complications, the US CDC reported two premature membrane ruptures as well as spontaneous abortions, both related to the H1N1 Influenza infection. As discovered through telephone interviews, the H1N1 Influenza infection was not encountered in any of the babies that the women delivered during their in-patient monitoring period. However, potential fetal complications such as neural tube defects, seizures, encephalopathy, and death related to high febrile states seen during the progression of infection should not be forgotten [15].

The limitation to our study is that it only involved a small number of cases.

To summarize, we can say that H1N1 Influenza A infections in pregnant women may cause significant maternal and fetal complications. We found that the disease was more dangerous for patients at an advanced gestational age, during multifetal pregnancies, or with co-morbid disorders. In these cases, a more detailed physical and obstetric examination and early treatment are important in the prevention of maternal-fetal morbidity and mortality.

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